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Hyperglycemia during tuberculosis treatment increases morbidity and mortality in a contemporary cohort of HIV-infected patients in Rio de Janeiro, Brazil

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ABSTRACT

Background: Hyperglycemia occurs in tuberculosis (TB), but the long-term impact is unknown. We estimated the prevalence of hyperglycemia and compared the TB treatment outcomes and 1-year mortality rate according to the glycemic status noted during TB treatment.
Methods: We conducted a retrospective cohort analysis of adult patients who had TB and HIV coinfection and started receiving TB treatment at the Instituto Nacional de Infectologia Evandro Chagas, Brazil, between 2010–2015. Diabetes Mellitus (DM) and hyperglycemia were defined according to the American Diabetes Association. After excluding for known DM at baseline, the proportion of participants who developed new-onset DM after TB treatment was assessed. TB outcome was classified as successful or adverse (i.e., treatment failure, abandonment, and death). Kaplan–Meier survival curves were compared by the log-rank test based on the glycemic status of patients. Multivariate Cox regression models were used to assess the association between hyperglycemia and 1-year mortality. Two-sided p values < 0.05 were considered statistically significant.
Results: We identified 414 euglycemic patients (87.5%), 49 hyperglycemic patients (10.3%), and 10 patients with known DM (2.1%). Diabetic patients were older compared to the euglycemic and hyperglycemic patients (47.9 vs. 37 vs. 39.7 years, respectively, $p = 0.001$). Diabetic patients frequently had cavitation on chest image compared to hyperglycemic and euglycemic patients (50% vs. 23.4% vs. 15.3%, $p = 0.007$, respectively). Hyperglycemic patients had more new-onset DM at follow-up compared to euglycemic (22 vs. 1; $p < 0001$). Hyperglycemia was associated with adverse outcomes (71.4% vs. 24.6%, $p < 0.0001$) compared to euglycemia. Crude 1-year mortality was significantly higher in patients with hyperglycemia compared with euglycemia (48.9% vs. 7.9%; unadjusted HR: 5.79 (3.74–8.96)). In the adjusted Cox models, hyperglycemia remained a significant factor for increased 1-year mortality (adjusted HR: 3.72 (2.17–6.38)].
Conclusions: Hyperglycemia frequently occurs in HIV-infected patients who commence TB treatment, and it increases the risks of adverse TB outcomes and 1-year mortality. Glucose testing during TB treatment detects patients at risk of adverse outcomes.

Introduction

Tuberculosis–a disease caused by the *Mycobacterium tuberculosis* complex–is the leading cause of death among people infected with the human immunodeficiency virus (HIV), accounting for one in five HIV-related deaths (WHO, 2016). The association of tuberculosis (TB) and diabetes mellitus (DM) is of great importance due to the detrimental effects of DM in patients with TB (Girardi et al., 2017). Diabetes mellitus increases the risk of TB and relapse after TB treatment by a factor of approximately three and four, respectively (Jeon and Murray, 2008) and doubles the risk of the combined outcome of therapy being failure and death (Baker et al., 2011). Furthermore, a study has found that the detrimental

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association between those conditions (TB & DM) remains among individuals infected and not infected with HIV (Oni et al., 2017).

In contrast, TB induces a state of secondary hyperglycemia and insulin resistance in individuals with or without a history of DM (Oluboyo and Erasmus, 1990; Jawad et al., 1995; Tabarsi et al., 2014). Hyperglycemia is a marker of illness severity and a well-recognized predictor of mortality across a diverse spectrum of conditions, including pneumonia (McAlister et al., 2005), sepsis (van Vught et al., 2016), and critical illness (van den Berghe et al., 2001; Krinsley, 2003). In a case-control study, investigators found that TB patients with hyperglycemia at enrolment are at a higher risk of short-term adverse outcomes (Boillat-Blanco et al., 2016). In another study the presence of hyperglycemia during TB did not influence the treatment outcomes (Tabarsi et al., 2014).

The association between TB outcome and the presence of hyperglycemia has been evaluated by cross-sectional studies, resulting in an overestimation of DM during the initial TB treatment (Kibirige et al., 2013; Moreno-Martinez et al., 2015; Bailey et al., 2016; Workneh et al., 2016). Moreover, the long-term impact of hyperglycemia on TB outcome is unknown, particularly in the context of HIV co-infection. Therefore, we evaluated the prevalence of hyperglycemia among patients co-infected with HIV and TB who started anti-tuberculosis treatment in Rio de Janeiro, Brazil. Additionally, we compared the TB treatment outcome and 1-year mortality rate according to the glycemic status of patients during TB treatment.

Methods

Study setting

Instituto Nacional de Infectologia Evandro Chagas (INI) is a regional reference center for the research and care of HIV-infected patients in Rio de Janeiro, Brazil. It has a clinical cohort of more than 9000 HIV-infected subjects in active follow-up. Further details about the cohort have been described elsewhere (Grinsztejn et al., 2013). INI offers an outpatient facility, an emergency department, a day-clinic, and an inpatient care unit (comprised of a ward and a 4-bed intensive care unit) and is funded by the Brazilian National Health Care System. A longitudinal database is maintained prospectively on in-hospital and outpatient clinical information on patients receiving care. Patients received free treatment for TB/HIV co-infection and physicians followed the Brazilian national guidelines for the treatment of TB and HIV infection (Brasil, 2011; Brasil, 2015).

Study population

We included consecutive, HIV-infected adults (≥18 years) registered at the HIV INI cohort who had started TB treatment (based on clinic-radiological features or positive acid-fast bacilli smear from the sputum or extra-pulmonary samples) during the period from January 1, 2010 to December 31, 2015. We then followed those patients until December 1, 2016, to the date of death, last clinical visit, or day of loss of follow-up, whichever occurred first. Patients who were pregnant at the time of TB treatment initiation, those who received TB treatment outside INI, or those still undergoing treatment were excluded from the analysis.

Selection of study sample

The original dataset contained information on each TB episode experienced by individual patients. Each patient record showed at least one episode and possible additional episodes if the treatment scheme was changed (i.e., failed TB treatment) or if the patient re-started treatment after abandoning it once (i.e., no follow-up for more than two months). In this study, we analyzed only the first episodes of TB for each patient; therefore, the unit of analysis was each patient.

Data collection

Sociodemographic, clinical, laboratory, microbiology, and TB treatment variables were extracted from the patient's medical records. Furthermore, variables related to HIV infection such as the category of acquisition, time since diagnosis, highly active antiretroviral therapy (HAART) status, and immuno-virological parameters were also extracted. Information related to potential co-morbidities during TB treatment that could influence the outcome such as hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection, smoking, malnutrition, and dyslipidemia was extracted. Complete blood counts, C-reactive protein (CRP) levels, a lipid panel, liver function tests, creatinine, and albumin levels were measured at the time of TB enrolment. Experienced radiologists evaluated the chest images for findings such as the presence of cavitation and a miliary pattern. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. Identification of *Mycobacterium tuberculosis* complex in culture-positive cases was conducted using biochemical and immune-chromatography methods (SD BIOLINE, TB Ag MPT64 rapid®, Standard Diagnostics, Gyeonggi-do, the Republic of Korea) (Fandinho et al., 1997). Additionally, testing for drug resistance was done for the first-line TB drugs using the proportion method (Brasil, 2008).

Operational definitions

The confirmation of the diagnosis of TB was primarily based on an initial positive acid-fast bacilli (AFB) smear from the sputum or extra-pulmonary samples, followed by any of the following tests: mycobacterial culture, histopathology, and in some cases, was supported by Xpert® MTB/RIF testing (Cepheid Solutions, Sunnyvale, CA, USA). Alternatively, suspected cases were empirically treated based on suggestive clinical symptoms coupled with an abnormal chest image. Patients with TB were included if it was their first diagnosis of the disease (i.e., new TB cases) or if the patient had a history of completed TB treatment but presented with new symptoms suggestive of TB (i.e., recurrent TB). We classified the TB according to the status of the AFB smear at the time of presentation (i.e., smear positive or negative) and area that the disease was confined to (i.e., pulmonary or extra-pulmonary disease). Mycobacteremia was defined as the positive growth of *Mycobacterium tuberculosis* in blood specimens.

HCV co-infection was defined by the presence of HCV antibodies, HBV by positive hepatitis B surface antigen, and dyslipidemia as LDL > 159 and/or HDL < 40 mg/dl. Malnutrition was determined as being underweight at the time of patient enrolment (BMI < 18.5 kg/m^2).

Steroid administration (either orally or intravenously) was obtained from data on prescriptions filled during TB treatment.

Recent HIV diagnosis was defined as an HIV diagnosis within two months of TB diagnosis.

TB resistance refers to TB illness with documented resistance to any of the four drugs tested on the patient (isoniazid, rifampin, streptomycin, and ethambutol).

The overall TB treatment outcome was classified as successful or adverse. Successful treatment refers to cured infection or completed TB treatment. The adverse outcome includes treatment failure, treatment discontinuation, and death due to any cause. Treatment failure was indicated by smear or culture positivity at or after five months of anti-TB treatment.

TB-related hospitalization was defined as a hospital admission related to TB treatment, anti-TB treatment toxicity, or a complication secondary to TB. All diagnoses listed in the discharge report were revised, and the admissions were further classified according to the presence of other opportunistic conditions. Hospitalizations in which the primary cause of admission was not TB were excluded. Among hospitalized patients, the proportion of intensive care unit (ICU) admissions and hospital readmissions were computed.

Longitudinal evaluation of glycemic changes and proportion of diabetes during follow-up

Glucose testing (i.e., fasting glucose plasma) is part of the routine work-up for co-infected HIV/TB patients in our institution. A longitudinal analysis of changes in blood glucose after TB treatment initiation was performed during a period of six-years [2010–2016]. After excluding those with known DM, we assessed the proportion of participants who developed new-onset DM after TB treatment initiation during the study period. Blood glucose testing (Dimension® Clinical Chemistry System, SIEMENS Healthcare Diagnostics Inc., Malvern, PA, USA) was conducted by measuring the fasting plasma glucose and the glycated hemoglobin (A1c) level using anticoagulated plasma specimens. In some subjects, the blood glucose levels before TB treatment initiation were available.

Diagnosis of diabetes mellitus, hyperglycemia, and euglycemia

We defined DM according to the current American Diabetes Association guideline (Chamberlain et al., 2016). The term "diabetes mellitus" was defined as a condition of a known history of diabetes before TB treatment initiation or the use of oral antidiabetic medication or insulin as chronic medication. Prior use of metformin alone was deemed insufficient to consider DM due to the wide range of other therapeutic indications for metformin. The same criteria were used to define new-onset DM at follow-up.

Hyperglycemia was defined as at least two blood glucose measurements $\geq$ 126 mg/dl in a fasting state during the entire period of TB treatment. To determine the normalization of glycemia after initial hyperglycemia episode, at least two glucose measurements $<$ 126 mg/dl were required. Alternatively, euglycemia was defined as measurements of blood glucose $<$ 126 mg/dl.

For clarity, the term "hyperglycemia" refers to a transient, often dynamic disorder characterized by an elevation in blood glucose concentration that responds to changes in the disease course, and is usually restricted to patients without previous evidence of diabetes (Dungan et al., 2009).

For patients with a previous diagnosis of DM, the time of DM diagnosis, the type of treatment, and the glucose control levels were documented.

Metformin use among patients in the cohort was obtained from data on prescriptions filled during TB treatment.

Outcomes

First, we estimated the prevalence of hyperglycemia during TB treatment. Second, we compared TB treatment outcomes and the 1-year mortality rate after TB treatment initiation according to the glycemic status of patients.

Statistical analysis

Descriptive analyses were performed to characterize the distributions of several variables. Chi-square test was used to compare categorical variables between the study groups (i.e., euglycemia, hyperglycemia, and DM). Continuous variables were compared between the study groups using analysis of variance or Kruskal–Wallis test if those were found to be normally or non-normally distributed, respectively.

Kaplan–Meier survival curves were compared between those with hyperglycemia and euglycemia during TB treatment using the log-rank test. Multivariable Cox proportional hazard models were used to determine the association between hyperglycemia during TB treatment and 1-year mortality. For patients who were lost to follow-up before one year, the follow-up time until their last known assessment of vital status was determined, and the data were censored after that. The crude associations between death and hyperglycemia were estimated by hazard ratios (HR) and 95% confidence intervals (CI). The covariates that were univariately associated with 1-year mortality and those that have been shown to predict mortality – gender, age, TB-related hospitalization, steroid use during TB treatment, cluster of differentiation ($CD4^+$) cell count, baseline hemoglobin, and albumin – were used in those models. Further, those confounders were included in a stepwise manner and remained in the models if the adjusted association differed from the unadjusted HR by more than 10%. We dealt with missing data using the listwise deletion method (or complete case analysis). A two-tailed p-value $<$ 0.05 was considered statistically significant. The SPSS (version 23.0, IBM statistics, Chicago, IL, USA) and GraphPad Prism (version 6.0, GraphPad Software, San Diego, CA, USA) software's were used for all statistical analyses.

Results

Between 2010 and 2015, we identified 614 TB episodes in patients that were actively followed in the HIV INI cohort (Figure 1). We further limited our sample to patients with first episodes of TB, which corresponded to 504. Thirty-one subjects were excluded from the study for the following reasons: 28 were treated for TB outside our unit, two were undergoing treatment for TB, and one was pregnant at the time of TB treatment initiation.

Our final study sample consisted of 473 individuals. The characteristics of the cohort are described in Table 1. The mean age of patients was 37.5 ($\pm$10.3) years with a predominance of male patients (68.5%) in the study. The ethnicity of 68.7% study participants was non-white, and over 60% patients had received a formal education of up to 8-years. We confirmed microbiologically the diagnosis of TB in 78% patients and nearly half presented with pulmonary TB (44.6%). The median time from HIV diagnosis to TB treatment initiation was 11 (interquartile range: 0–87) months, and approximately one-third of the patients had received a recent HIV diagnosis (30%).

Based on the analyses of glucose changes during TB treatment, we identified 414 euglycemic subjects [87.5%, 84.1–90.3], 49 hyperglycemic subjects without a prior history of DM [10.3%, 7.8–13.5], and 10 known diabetic subjects [2.1%, 1–3.9] (Supplementary Figure 1A). The median time from TB treatment initiation to the diagnosis of hyperglycemia was 30 (interquartile range: 5–101) days. There was no difference in the proportion of subjects already receiving highly active antiretroviral therapy (HAART) at the time of TB diagnosis between euglycemic, hyperglycemic, and diabetic subjects (50% *vs.* 46.9% *vs.* 70%, p = 0.41, respectively). The mean time from TB diagnosis to HAART initiation for those who were HAART-naïve at time of TB diagnosis was 1.54 $\pm$ 3.7 months. Efavirenz-based HAART was the anchor drug of choice in the majority of participants (65.4%).

Diabetic patients were older compared to the euglycemic and hyperglycemic patients (47.9 *vs.* 37 *vs.* 39.7 years, respectively, p = 0.001). The sex distribution (male = 67.6% *vs.* male = 75.5% *vs.* male = 70%, p = 0.53) and BMI values (20.2 $\pm$ 3.5 *vs.* 19.2 $\pm$ 3.9 *vs.* 19.4 $\pm$ 2.72 kg/m^2, p = 0.18) were similar between the euglycemic, hyperglycemic, and diabetic groups. The hyperglycemic group had

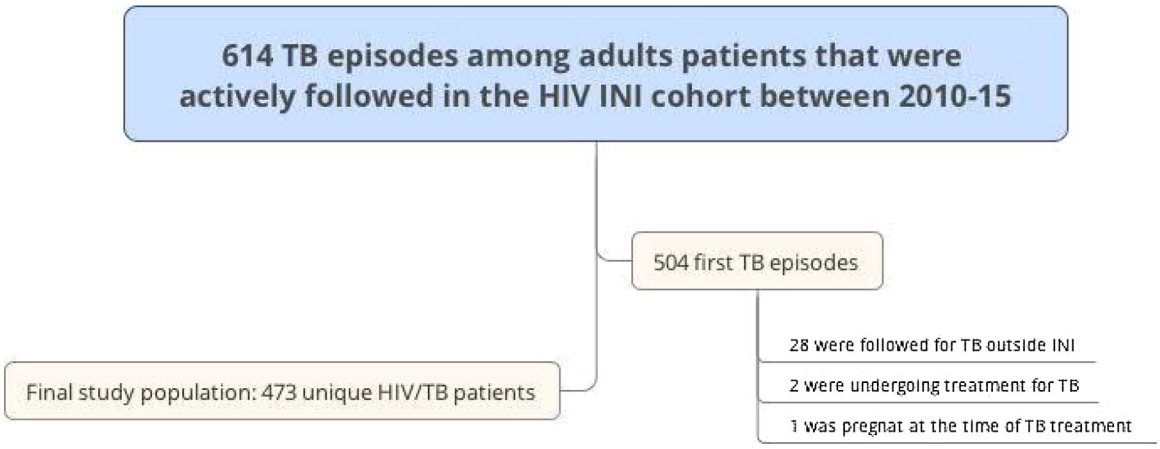


Figure 1. Flowchart of the study population.
Legend: study population selection methodology. HIV stands for human immunodeficiency virus, INI Instituto Nacional de Infectologia Evandro Chagas, TB tuberculosis.

a shorter TB treatment duration (4.43 ± 3.4 *vs.* 6.49 ± 3.8 *vs.* 7.3 ± 3.26 months, $p = 0.001$) and were more likely to have mycobacteremia and dyslipidemia as compared with euglycemic and diabetic groups (29.8% *vs.* 13.3% *vs.* 14.3%, $p = 0.01$; 90% *vs.* 67.5% *vs.* 42.9%, $p = 0.002$, respectively) (Supplementary Figure 1B and 1C). Furthermore, patients with DM more frequently had cavitation on the chest image compared to hyperglycemic and euglycemic groups (50% *vs.* 23.4% *vs.* 15.3%, $p = 0.007$, respectively). Steroid use was documented in 49 (10%) patients of the cohort, and was more frequently prescribed in hyperglycemic compared to euglycemic subjects (65.3% *vs.* 34.7%, $p < 0.0001$). Among the 473 patients in the cohort, 12 (2.5%) received metformin.

Table 1
Characteristics of patients with HIV/TB followed at INI HIV cohort (2010–2015).

Characteristic	All TB/HIV ($n = 473$)	Euglycemia ($n = 414$)	Hyperglycemia ($n = 49$)	DM ($n = 10$)	Overall *p*-value
Age (years), mean ± SD	37.5 ± 10.3	37 ± 10	39.7 ± 11	47.9 ± 5.13	**0.001**
Male – n (%)	324 (68.5)	280 (67.6)	37 (75.5)	7 (70)	0.53
Ethnicity – n (%)					
White	146 (32.3)	132 (32.5)	11 (22.9)	3 (30)	0.40
Non-White	320 (68.7)	276 (67.6)	37 (77.1)	7 (70)	
Transsexual – n (%)	23 (4.9)	20 (4.8)	3 (6.1)	0	0.71
Schooling (years) – n (%)					
Uneducated	23 (5.1)	18 (4.5)	5 (10.6)	0	0.27
1–8	276 (61.1)	240 (60.5)	32 (68.1)	4 (40)	
9–12	121 (26.8)	109 (27.5)	9 (19.1)	3 (30)	
>12	32 (7.1)	30 (7.6)	21 (2.1)	1 (10)	
HIV exposure category – n (%)					
Heterosexual	248 (59.9)	220 (60.3)	22 (56.4)	6 (60)	0.43
Homosexual	104 (25.1)	93 (25.5)	10 (25.6)	1 (10)	
Bisexual	45 (10.9)	38 (10.4)	5 (12.8)	2 (20)	
IDU	8 (1.9)	7 (1.9)	0	1 (10)	
Other	9 (2.1)	7 (1.9)	2 (5.1)	0	
BMI (kg/m^2), mean ± SD[a]	20 ± 3.56	20.21 ± 3.52	19.23 ± 3.91	19.4 ± 2.72	0.18
Time from HIV diagnosis to TB treatment initiation (months), median (IQR)	11 (0–87)	10 (0–86)	18 (0–84)	102 (15–184)	0.16
Time from HAART initiation to TB treatment initiation (months), mean ± SD	62.3 ± 64.6	61.3 ± 63.9	61 ± 66.7	98.14 ± 78.5	0.33
Recent HIV diagnosis – n (%)	142 (30)	123 (29.7)	17 (34.7)	2 (20)	0.60
HAART experience – n (%)	238 (50.3)	208 (50.2)	23 (46.9)	7 (70)	0.41
TB history – n (%)	105 (22.2)	92 (22.3)	11 (22.4)	2 (20)	0.98
Laboratory confirmed TB – n (%)	369 (78)	321 (77.5)	39 (79.6)	9 (90)	0.61
Pulmonary TB – n (%)	211 (44.6)	188 (45.4)	17 (34.7)	6 (60)	0.22
Mycobacteremia – n (%)[a]	56 (15.5)	41 (13.3)	14 (29.8)	1 (14.3)	**0.01**
AFB+ smear – n (%)[a]	210 (46.2)	178 (44.9)	25 (51)	7 (70)	0.22
Cavitary disease – n (%)	78 (16.9)	62 (15.3)	11 (23.4)	5 (50)	**0.007**
Miliary pattern on chest image – n (%)	72 (15.2)	64 (15.5)	8 (16.3)	0	0.39
Resistant TB – n (%)	49 (17.9)	41 (17.1)	7 (25)	1 (20)	0.58
TB treatment duration (months), mean ± SD	6.3 ± 3.85	6.49 ± 3.85	4.43 ± 3.48	7.3 ± 3.26	**0.001**
Co-morbidities – n (%)					
Malnutrition	144 (34.8)	120 (33.4)	21 (44.7)	3 (30)	0.30
Smoking	209 (49.5)	185 (50.3)	19 (43.2)	5 (50)	0.67
HCV	32 (7.3)	28 (7.6)	2 (4.7)	1 (12.5)	0.69
HBV	26 (5.5)	20 (4.8)	4 (8.2)	2 (20)	0.07
Dyslipidemia[a]	237 (69.9)	195 (67.5)	39 (90.7)	3 (42.9)	**0.002**

AFB stands for acid-fast bacilli, BMI body mass index, DM diabetes mellitus, HAART highly active antiretroviral therapy, therapy, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, IDU injecting drug user, IQR interquartile range, TB tuberculosis, SD standard deviation. Overall *p* values are *p* values generated to identify differences between the three groups by using an analysis of variance, a Kruskal–Wallis or a chi-square test. *p* values <0.05 are in bold.
[a] BMI (12.5%); AFB+ smear (3%); mycobacteremia (23%); dyslipidemia (28%): percentages of observations missing for each variable.

Table 2
Laboratory features at baseline of HIV/TB patients followed at INI HIV cohort (2010–2015).

Baseline laboratory tests	Euglycemia	Hyperglycemia	DM	Overall *p*-value
Glucose (mg/dl), median (IQR)	87 (79–97)	112 (82–137)	178 (129–205)	<**0.0001**
AST (U/L), median (IQR)	87 (79–97)	49.5 (35–84)	26 (22–57)	0.05
ALT (U/L), median (IQR)	39 (28–56)	36 (27–53)	28 (21–44)	0.12
ALP (U/L), median (IQR)	141 (99–243)	159 (102–218)	122 (100–147)	0.58
Total bilirubin (mg/dl), median (IQR)	0.4 (0.3–0.60	0.4 (0.3–0.7)	0.4 (0.3–0.7)	0.86
Creatinine (mg/dl), median (IQR)	0.85 (0.72–1.05)	1.02 (0.85–1.37)	0.96 (0.73–1.04)	<**0.0001**
Hemoglobin (g/dl), mean ± SD[a]	10.2 ± 2.3	9.4 ± 2.35	10.6 ± 2.13	0.06
White blood cell (cells/μL), median (IQR)	6130 (4280–8610)	6860 (4800–8560)	6.685 (4.090–10.160)	0.47
Platelet (μL), median (IQR)	295×10^3 (225×10^3–375×10^3)	292×10^3 (170×10^3–350×10^3)	301×10^3 (201×10^3–428×10^3)	0.23
Albumin (mg/dl), mean ± SD[a]	2.6 ± 0.82	1.8 ± 0.56	2.4 ± 0.86	<**0.0001**
CRP (mg/dl), median (IQR)[a]	6.49 (1.9–14.2)	11.35 (3.89–20.2)	8.11 (5.86–13)	**0.02**
TC/HDL ratio, median (IQR)	4.48 (3.55–6.19)	6.27 (4.74–8.88)	3.52 (2.81–7.59)	<**0.0001**
TG/HDL ratio, median (IQR)	4.48 (3.55–6.19)	6.08 (3.76–14.4)	2.65 (1.68–6.54)	<**0.0001**
Nadir $CD4^+$ (cells/μl), median (IQR)	90 (27–197)	47 (20–78)	159 (62–295)	**0.02**
$CD4^+$ (cells/μl), median (IQR)[a]	146 (48–336)	70 (25–205)	323 (129–695)	**0.002**
$CD8^+$ (cells/μl), median (IQR)	653 (379–1100)	403 (153–715)	610 (519–862)	**0.001**
CD4/CD8 ratio, median (IQR)	0.20 (0.09–0.42)	0.19 (0.11–037)	0.27 (0.21–0.69)	0.21
HIV VL (logs), median (IQR)	4.70 (3.83–5.29)	4.20 (3.25–5.31)	4.62 (4.11–5.36)	0.47

A1c stands for glycated hemoglobin; ALT alanine aminotransferase, ALP alkaline phosphatase, AST aspartate aminotransferase, $CD4^+$ cluster of differentiation 4, $CD8^+$ cluster of differentiation 8, CRP C-reactive protein, HIV VL HIV viral load; IQR interquartile range, SD standard deviation TC/HDL total cholesterol/HDL cholesterol ratio, TG/HDL triglycerides/HDL cholesterol ratio. Overall *p* values are *p* values generated to identify differences between the three groups by using an analysis of variance or a Kruskal–Wallis test. *p* value <0.05 are in bold.

[a] Hemoglobin (4%); albumin (18%); creatinine (7%) CRP (46.9); $CD4^+$ (10%): percentages of observations missing for each variable.

We then compared the groups in terms of the laboratory parameters obtained at treatment enrolment (Table 2). Supplementary Figures 2 and 3 show the main laboratory parameters stratified according to glycemic status of patients during TB treatment and include previous known diabetics. Individuals who were diabetic and hyperglycemic had higher glucose levels compared to euglycemic controls (178 [129–205] *vs.* 112 [82–137] *vs.* 87 [79–97] mg/dl, $p < 0.0001$, respectively). Patients with hyperglycemia had higher serum creatinine (1.02 [0.85–1.37] *vs.* 0.96 (0.73–1.04) *vs.* 0.85 [0.72–1.05] mg/dl, $p < 0.0001$) and CRP levels (11.35 [3.89–20.2] *vs.* 8.11 (5.86–13) *vs.* 6.49 [1.9–14.2] mg/dl, $p = 0.02$) compared to patients with DM and euglycemia.

In order to evaluate the immuno-virological outcome through the course of TB treatment, we compared the $CD4^+$ cell counts and HIV viral loads at baseline and 1-year after the start of TB therapy (Supplementary Figures 4 & 5).

For the ten known diabetic patients, the median time of diabetes diagnosis was recorded as 7.6 years, and therapy consisted of oral anti-hyperglycemic drugs, a combination of oral anti-hyperglycemic drugs and insulin, insulin monotherapy, and lifestyle measures in four, three, two, and one subjects, respectively. Glycemic control was found to be inadequate (fasting plasma glucose ≥126 mg/dl) and adequate (<126 mg/dl) in eight and two patients, respectively.

Longitudinal evaluation of glycemic changes and proportion of diabetes during follow-up

Fifty-five percent of the patients had blood glucose levels measured immediately before TB treatment initiation. The mean glucose concentration before TB treatment onset was higher in the diabetic group compared to the hyperglycemic and euglycemic groups (175 ± 56 *vs.* 86 ± 14 *vs.* 88 ± 20 mg/dl, $p < 0.001$, respectively). We then followed the patients after TB treatment initiation from 2010 to 2016 (mean follow-up time: 36.6 ± 24.9 months). After excluding patients with previously known DM ($n = 10$), those who died during TB treatment ($n = 57$), and those who were lost to follow-up ($n = 27$), we analyzed the presence of new-onset DM at the end of the study period (Supplementary Figure 6). A total of 22 (32%) subjects developed DM in the hyperglycemic group compared to 1 (0.28%) in the euglycemic group during follow-up. There was an association between glucose status during TB treatment and presence of new-onset DM at the end of follow-up (i.e., 22 *vs.* 1; $p < 0.0001$).

Treatment outcomes and 1-year mortality rate according to patient glycemic status

We next compared the TB treatment outcomes according to the glycemic status of patients (Table 3). The hyperglycemic group experienced unfavourable events (i.e., treatment failure, loss to follow-up, death) more frequently after treatment initiation compared to the euglycemic group (71.4% *vs.* 24.6%, $p < 0.0001$) (Figure 2A). Moreover, hyperglycemia was associated with a higher proportion of TB-related hospitalization than that recorded for euglycemic patients (83.7% *vs.* 52.9%, $p < 0.0001$) (Figure 2B). Furthermore, the length of hospitalization (45.5 [20.5–72.5] *vs.* 14 [8–24] days, $p < 0.0001$) and the proportion of ICU admissions were higher in the hyperglycemic group than in the euglycemia patient group (72.5% *vs.* 16.6%, $p < 0.0001$) (Figure 2C).

The indicators for hospital admission in the hyperglycemic group of patients were treatment initiation (77.5%), TB-related complications (17.5%), and other indications (5%). The majority of patients in the hyperglycemic group were diagnosed with TB upon hospital admission (77.5%), and 22.5% were admitted during anti-TB therapy. Opportunistic infections occurred in 26 (53%) hyperglycemic subjects and included *Pneumocystis jiroveci* pneumonia (9), neurotoxoplasmosis (5), *Cryptococcus neoformans* meningitis (4), disseminated histoplasmosis (4), *Cytomegalovirus* infection (3), Kaposi's sarcoma (2), and one each for aspergillosis, *Mycobacterium avium* complex, and JC infection. In three admissions, more than one opportunistic infection coincided with TB diagnosis. Similar to the findings in the hyperglycemic group, euglycemic subjects were admitted for TB treatment initiation (75.4%), TB-related complications (10.9%), anti-TB drug toxicity (9%), and other indications (4.7%). Opportunistic conditions occurred in 21 (5%) euglycemic patients and included *Pneumocystis jiroveci* pneumonia (7), *Cytomegalovirus* infection (3), Kaposi's sarcoma (3), neurotoxoplasmosis (3), *Cryptococcus* infection (2), histoplasmosis (2), cryptosporidiosis (1), esophageal candidiasis (1), and disseminated sporotrichosis (1). In four admissions, more than one opportunistic condition co-occurred with TB diagnosis.

Table 3
Tuberculosis outcome according to glycemic status during tuberculosis treatment.

	Euglycemia ($n = 414$)	Hyperglycemia ($n = 49$)	Known DM ($n = 10$)	p-value
TB outcome – n (%):				**0.0001**
Successful	312 (75.4)	14 (28.6)	8 (80)	
Adverse	102 (24.6)	35 (71.4)	2 (20)	
Pattern of TB outcome – n (%):				**0.0001**
Cure/completed TB treatment	309 (74.6)	14 (28.6)	8 (80)	
Death	31 (7.5)	25 (51)	1 (10)	
Lost to follow-up	72 (17.4)	10 (20.4)	1 (10)	
Treatment failure	2 (0.5)	0	0	
Hospitalization – n (%)	219 (52.9)	41 (83.7)	6 (60)	**0.0001**
Length of hospitalization (days) median (IQR)	14 (8–24)	45.50 (20.5–72.5)	31 (15–39)	**0.0001**
ICU admission – n (%)	35 (16.6)	29 (72.5)	1 (6.7)	**0.0001**
Readmission – n (%)	43 (19.7)	13 (31.7)	2 (33.3)	0.18

ICU stands for intensive care unit, IQR interquartile range, TB tuberculosis. p values <0.05 are in bold.

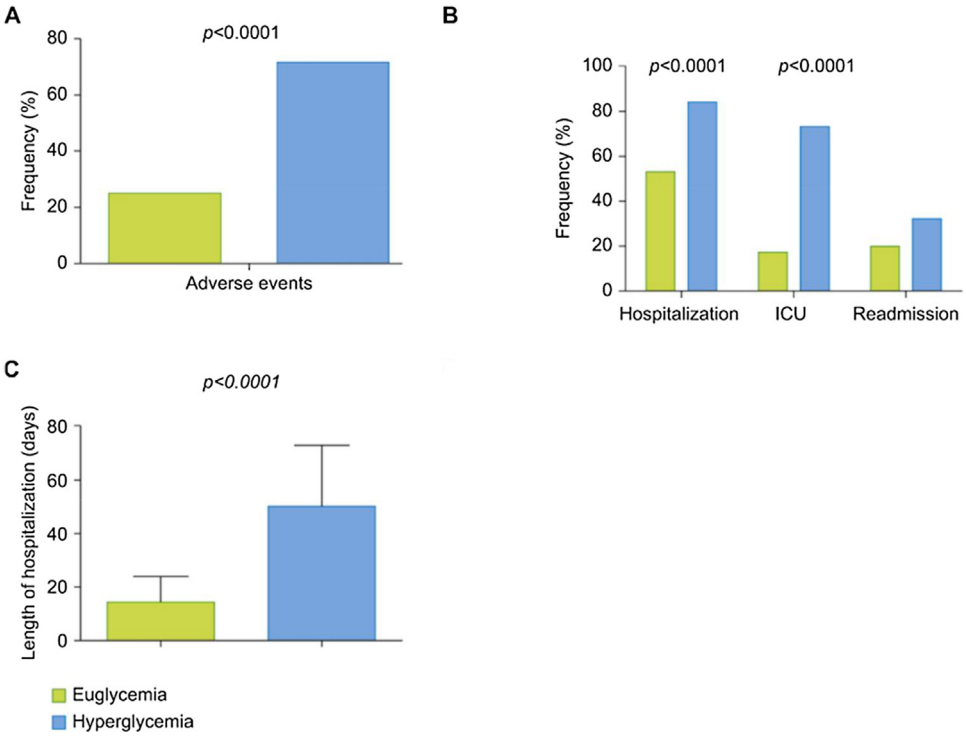


Figure 2. Hyperglycemia during tuberculosis treatment is associated with increased morbidity.
Legend: (A) Frequency of total adverse outcomes (treatment failure, lost to follow-up, death due to any cause) upon anti-tuberculosis treatment initiation. (B) Frequencies of hospitalization, intensive care unit admission, and readmission after anti-tuberculosis treatment initiation. (C) Length of hospitalization (days).

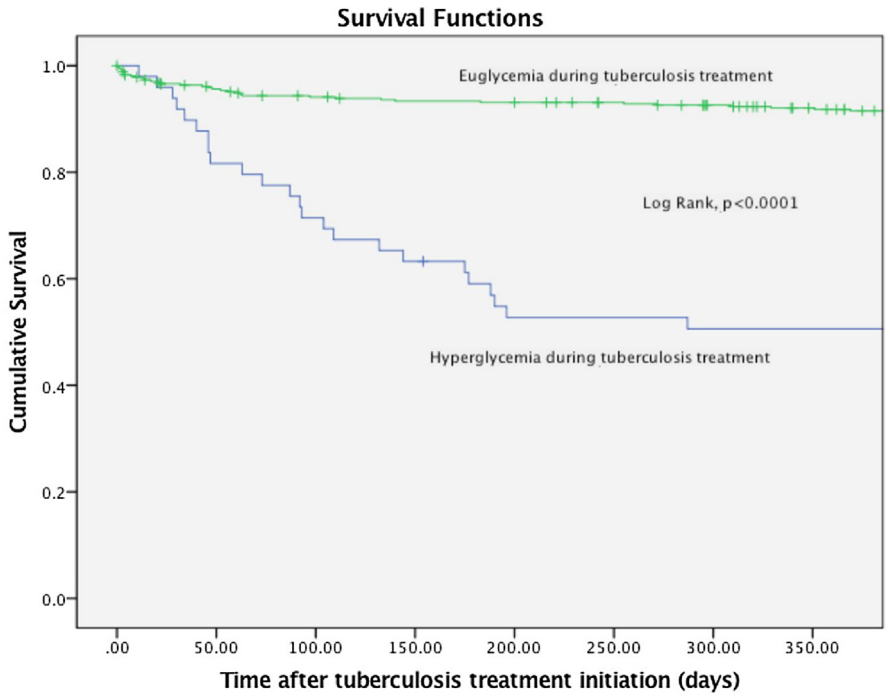
The proportion of opportunistic infections was higher in the hyperglycemic compared to euglycemic group (53% *vs.* 5%, $p < 0.0001$). The deleterious effects of hyperglycemia during TB treatment remained significant, even when compared to those with known DM before the TB diagnosis (Table 3).

The crude 1-year mortality was significantly higher in patients with hyperglycemia compared with euglycemic patients [48.9% *vs.* 7.9%; unadjusted HR: 5.79 (3.74–8.96)]. Similarly, the mean survival time after treatment initiation was lower in the hyperglycemic group compared to the euglycemic group (963 [95% CI 683–1242] *vs.* 2103 [95% CI 2025–2182] days). Figure 3 shows the survival curves according to glycemic status. In the crude analysis, steroid use during TB treatment was associated with mortality (OR: 2.08 [95% CI 1.48–2.92]). We fitted two multivariable models adjusting for the potential confounders, and either one of the two models,; hyperglycemia was associated with an increased risk of mortality at 1-year after TB treatment initiation compared to patients with euglycemia (Supplementary Figure 7 & Supplementary Tables 1 & 2).

Discussion

We found that transient hyperglycemia frequently occurs in HIV-infected patients who started TB treatment in Rio de Janeiro, Brazil, and it increased the risks of adverse TB outcomes and 1-year mortality.

Our study explores the association between hyperglycemia during TB therapy and long-term mortality in patients co-infected with HIV and TB. The study population was well defined, and TB was confirmed in almost 80% patients, with positive culture results in 67% of patients. Moreover, we examined the clinical and laboratory characteristics presented at disease enrolment that



	Euglycemia (*n*= 414)	Hyperglycemia (*n*= 49)
Mortality event observed	60	31
Cumulative probability		
50 days	0.95	0.81
100 days	0.94	0.71
150 days	0.93	0.63
200 days	0.93	0.52
250 days	0.93	0.52
300 days	0.92	0.50
365 days	0.91	0.50

Figure 3. Survival curve stratified according to the glycemic status during tuberculosis treatment.
Legend: Kaplan–Meier survival curves comparing 1-year mortality according to glycemic status during tuberculosis treatment. 365-days survival table is also shown. Log-rank test, $p < 0.0001$. Note that known DM subjects ($n = 10$) before onset of TB treatment were excluded of this analysis.

might be associated with hyperglycemia. Although we found that hyperglycemia was associated with new-onset DM at follow-up, we must interpret this finding with caution because (i) a proportion of hyperglycemic subjects did not have pre-TB glucose measurements and might represent undiagnosed diabetes; (ii) few patients developed DM in the follow-up, and therefore, we were unable to perform an adjusted analysis that would take into consideration other confounders such as duration of HAART use, HAART scheme, and BMI. Another explanation for the low proportion of patients presenting with new-onset DM in our study was the duration of follow-up. Diabetes mellitus is a chronic and slowly progressive disease, and its incidence risk might increase proportionally with the period of observation.

Similarly, we could not investigate the impact of DM on long-term mortality because our study was underpowered (i.e., limited DM sample group) to perform such analysis. Further, given that 80% of hyperglycemic patients had developed hyperglycemia during their hospitalization for TB, our findings reflect a more appropriate representation of known hospital-related hyperglycemia that is associated with deleterious outcomes in both ICU and non-ICU settings (Leonidou et al., 2007; Schuetz et al., 2012; Tiruvoipati et al., 2012; van Vught et al., 2016). Next, although we excluded patients treated for TB in other clinics, we cannot exclude with certainty that hyperglycemia was the result of interventions known to affect the glucose levels (i.e., co-administration of hyperglycemic and TB drugs; steroids; catecholamines). Herein, we attempt to correct this limitation by adjusting our analysis for steroid use during TB treatment. We found that the association between steroid use and mortality was nullified on multivariable analysis. Finally, blood glucose results measured by A1c testing were unavailable for some patients (i.e., 88% did not have baseline A1c results). As a result, we might have misclassified hyperglycemia in patients that had prevalent but unrecognized DM in the setting of an acute infectious insult. However, to limit the impact of this confounder, we verified the glucose levels before commencing TB treatment in 35/49 (71%) hyperglycemic patients to rule out prevalent DM in this latter group, and the mean glucose concentration before TB treatment initiation in the hyperglycemic group was 86 ± 14 mg/dl.

The negative impact of hyperglycemia during TB treatment shown in our study is consistent with a previous case-control study conducted in Dar es Salaam, Tanzania (Boillat-Blanco et al., 2016),

where the investigators concluded that fasting capillary glucose levels obtained at the time of TB enrolment of patients were significantly associated with an adverse TB outcome (adjusted OR: 3.32; 95% CI: 1.20–9.14). However, in that study, the median follow-up was five months after TB treatment initiation, and the proportion of HIV/TB co-infection was 32%. Here, we confirm that hyperglycemia affects mortality in the medium-term (i.e., our mean follow-up time: 36.6 ± 24.9 months), particularly in the setting of HIV/TB co-infection. In another study, conducted in Tehran, Iran, investigators found no associations between glucose status and treatment outcomes (Tabarsi et al., 2014). We hypothesized that differences in the relationship between hyperglycemia and TB treatment outcomes might be due to a number of reasons such as power of the study (i.e., larger sample size means higher probability to detect adverse TB outcomes), presence of effects modifiers (i.e., HIV, malnutrition, smoking, drug abuse), and the cut-off used to define hyperglycemia in each study. Therefore, further prospective studies with large numbers of patients are required.

Previous studies have shown that TB induced stress hyperglycemia (due to general inflammatory factors triggered by active TB), especially in the first months after treatment initiation, but thereafter, there is a return to a euglycemic state (Bloom, 1969; Seth et al., 1982; Oluboyo and Erasmus, 1990; Jawad et al., 1995; Basoglu et al., 1999; Tabarsi et al., 2014; Ogbera et al., 2015; Boillat-Blanco et al., 2016). Likewise, in our cohort, the median time from TB treatment initiation to hyperglycemia detection was 30 days, and 68% of those patients further normalized to a euglycemic state. The transitory hyperglycemia may also be explained by the occurrence of early phase hyperglycemia induced by rifampicin administration (Takasu et al., 1982; Sharma et al., 1986) or by steroid administration. Whatever the precise reason, this finding reinforces the need to repeat glucose measurements to confirm DM diagnosis.

Given the differences in the clinical and laboratory results among patients with hyperglycemia and euglycemia, we concur with the previous assumptions that hyperglycemia is an early surrogate marker of abnormal metabolic derangement and insulin resistance (i.e., higher proportion of dyslipidemia and higher concentration of Total Cholesterol/HDL and Triglycerides/HDL ratios) that is unmasked in the context of active TB disease (Dungan et al., 2009; Boillat-Blanco et al., 2016). Besides, those with hyperglycemia had evidence of severe TB illness reflected by the higher frequency of mycobacteremia in this group. Cumulatively, these data suggest that hyperglycemia during TB therapy involves a multifactorial mechanism including the patient's underlying glucose intolerance and severity of illness.

The interplay between DM and TB in HIV-infected individuals, especially in settings that are coupled with an HIV/TB epidemic, remains mostly unknown. Studies that addressed the association between DM and TB according to HIV status have produced conflicting results. In one study, investigators found no association between TB and DM in HIV-infected subjects (adjusted OR: 0.1, 95% CI: 0.01–1.8) compared to HIV-uninfected subjects (adjusted OR: 4.2, 95% CI: 1.5–11.6) (Faurholt-Jepsen et al., 2011). In another study, the presence of HIV co-infection was protective for TB/DM associations after adjustments for confounders (adjusted OR: 0.32,95% CI: 0.32–0.79) (Kibirige et al., 2013). Although the exact mechanism for this opposite effect of HIV remains to be elucidated, one explanation is the co-administration of co-trimoxazole, which has been found to cause hypoglycemia in HIV-infected subjects (Strevel et al., 2006). More research is needed to elucidate the strength of the interaction between TB and DM in HIV-infected patients.

Several studies have suggested that metformin augments protective host immune responses in both animal and human TB models (Restrepo, 2016). Metformin was found to reduce *M. tuberculosis* growth and improve pathology in mice, and its use was associated with decreased mortality and number of lung cavities in humans (Singhal et al., 2014; Degner et al., 2017). Our study was not designed to explore the effect of metformin on survival, but the fact that all metformin users in our cohort remained alive after TB treatment suggests a potential adjunct role for TB therapy in co-infected HIV patients.

The implications of our study findings are three-fold. First, routine blood glucose testing during TB treatment identified those at a higher risk of adverse TB outcome and mortality. Second, hyperglycemia during TB illness might detect those at a higher risk of developing DM later, after the completion of TB treatment. In theory, early identification of such individuals would facilitate access to care and treatment and would reduce DM disease complications. The efficacy and cost-efficacy of such screening programs for patients with hyperglycemia after TB remain to be addressed. Lastly, the optimal target for glucose management is not clear and further research should be conducted to investigate the impact of glucose-lowering interventions in this context.

In conclusion, hyperglycemia frequently occurs in HIV-infected patients who commence TB treatment, and it increases the risks of adverse TB outcomes and 1-year mortality.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

Ethical approval was obtained from the INI/FIOCRUZ Research Ethics Committee under the following registration: 61498516.8.0000.5262. Due to its retrospective study design, participants informed consent has been waived.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2017.12.014.

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